Remarks

Applicant thanks Examiner Hutson for a productive interview on Oct 23, 2007. The present Response is submitted in accordance with the discussions at that interview.

The only rejections outstanding in the present case are rejections for lack of written description and lack of enablement under 35 USC 112. The Examiner has taken the position, clarified in the interview, that Applicant had not previously recited with sufficient clarity structural elements that confer upon archeal DNA B polymerases an ability to incorporate acyclonucleotides as recited in the present claims.

In the interview, Applicant's representative proposed a claim structure reciting an overall degree of homology between claimed DNA polymerases and SEQ ID NO:4 (Vent™), and further reciting a particular sequence element that correlates with ability to incorporate acyclonucleotides. The Examiner indicated that such an approach would be helpful. The present claims, embodying that proposal, are therefore submitted for examination.

The present claims recite a method of incorporating acyclonucleotides into a nucleic acid by contacting a template nucleic acid (in the presence of primer and appropriate nucleotides) with a DNA polymerase that shows 30% (claims A and B) or 70% (claim C) overall identity with SEQ ID NO:4 and further includes a particular 15 amino acid sequence element. The recited 15 amino acid sequence element is the same element discussed in the interview and presented in the specification in Table 3.

The present specification well illustrates correlation between the sequence element recited in the present claims and the ability to incorporate acyclonucleotides. For example, the specification exemplifies incorporation by 4 different DNA polymerases, each of which shows at least 30% (indeed, at least 70%) overall identity with Vent™, and each of which has a 15 amino acid sequence that is identical to one of SEQ ID NOs: 5-22 (specifically, that is identical to one of SEQ ID NOs: 5, 6, 7 or 8). Comparison of the particular 15 amino acid sequence elements found in these DNA polymerases with one another reveals that the different elements differ from one another only by substitution of up to 3 amino acid residues (i.e., by up to 20%).

The present specification further illustrates that two other DNA polymerases that also show at least 30% (at least 70%) identity with Vent™ and have a 15 amino acid residue identical to one of SEQ ID NOs: 5-22 except for the substitution of a single residue (i.e., Vent™ 488L, which has a substitution of the first residue of SEQ ID NO:5 (L substituted for A) and 9°N/485L, which has a substitution of the first residue of SEQ ID NO:7 (L substituted for A).

Indeed, every DNA polymerase tested that meets the structural requirements of the presently submitted claims has the recited activity. Moreover, every DNA polymerase tested that meets the structural requirements of the presently submitted claims not only incorporated acyclonucleotides, but *preferentially* incorporated them; DNA polymerases lacking the recited structural requirements do not do so. For example, as discussed in the specification, the Klenow fragment of DNA polymerase I and the AMV reverse transcriptase both strongly *disfavor* acyclonucleotides (see, for example, page 5, line 34, which reads "approximately ten-fold higher concentrations of the acyclo derivatives were required to produce equivalent patterns"; see also page 19, line 22, which reads "Notably, those enzymes for which no significant sequence similarity is found (i.e., Family A DNA polymerases such as Taq) do not perform in similar ways".).

Of course, the cancellation of all pending claims renders moot the outstanding rejections. Nonetheless, Applicant addresses the rejections below, as if they were applied to the new claims.

Support for the New Claim Language

The present claims recite a method of using a DNA polymerase with certain structural characteristics. In particular, the DNA polymerase has an amino acid sequence that both:

(i) shows at least 30% (claim 32) or at least 70% (claim 33) overall identity with that of SEQ ID NO:4; and

(ii) includes a 15 amino-acid motif that is identical to a particular recited sequence (one of SEQ ID NOs 5-22 [claim 32], one of SEQ ID NOs 5-17 [claim 35]; one of SEQ ID NOs 5-8 [claim 37] except that it contains up to 3 amino acid substitutions as compared with the SEQ ID NO

is contacted with a template, primer, and nucleotides including acyclonucleotides, and is incubated so that the polymerase incorporates the acyclonucleotides. In claims 34, 36, and 38, the 15 amino acid motif is identical to a particular recited sequence; in claims 40, 41, and 42, it contains up to a single amino acid substitution.

Support for the description of useful DNA polymerases as showing "at least 30%" or "at least 70%) amino acid identity with SEQ ID NO:4 (i.e., with Vent™ DNA polymerase) can be found throughout the specification. In general, the specification emphasizes the structural homogeneity of relevant DNA polymerases (see, for example, page 3, line 11, etc). Moreover, the specification presents Table 3, which identifies a key sequence motif in relevant DNA polymerases and further illustrates the overall degree of sequence identity between each listed DNA polymerase and SEQ ID NO:4 (see column labeled "similarity"; as indicated in the Table legend, the first number in each row is percent identity with SEQ ID NO:4). As can be seen with reference to this Table, DNA polymerases that are not archeaon DNA B polymerases, and therefore are outside of the inventive scope (e.g., herpesvirus, human herpesvirus 2, human cytomegalovirus, human DNA polymerase alpha, phage T4, Taq™ DNA polymerase, Phage T7), show overall amino acid identity with SEQ ID NO:4 that is well below 30%.

The specification further explicitly calls out as of particular interest those DNA polymerases that show at least 70% overall amino acid identity with SEQ ID NO:4 (see, for example, page 19, lines 18-20, which state "Since *Pfu*, Deep Vent™, and 9°N™ DNA polymerases have greater than about 70% sequence identity with Vent™ DNA polymerase, other enzymes with equivalent or greater identity can reasonably be expected to perform as Vent™ (exo-) DNA polymerase in this invention". The particular appropriateness of such DNA polymerases is confirmed by reference to Table 3, in which the first twelve listed DNA polymerases all show this high degree of overall identity.

The present specification also points out the particular 15 amino acid motifs recited in the present claims; each is set forth in Table 3. Furthermore, even eyeball comparison of Table 3 reveals that, while modest variation is permitted, most motifs differ from each other only by substitution (i.e., not be deletion or addition), and almost all by 3 or fewer substitutions. Furthermore, the present specification also exemplifies "mutant" DNA polymerases (e.g., Vent™/488L; 9°N/485L) in which the 15 amino acid

motif differs by a single substitution from one presented in Table 3. Thus, the present specification provides solid support for the "identical except that it contains up to 3 (or up to 1) substitutions" language utilized in the present claims.

The specification further provides extensive description of reactions in which a DNA polymerase with the recited structural characteristics is incubated with template, primer, and nucleotides including acyclonucleotides, so that extension occurs (claim 32), and particularly so that preferential incorporation of acyclonucleotides is achieved (claim 39).

Written Description

The previously pending claims stood rejected for lack of written description. As explained above in the "Support for New Claims" section, the present specification includes extensive written description of the currently claimed invention.

Furthermore, Applicant submits that the relevant legal precedent confirms that the written description requirement is satisfied for the present claims in light of the present specification.

Applicant argued previously that the decision in *Invitrogen Corp v. Clontech Labs* 77 USPQ2d 1161 (Fed Cir 2005) required a finding that the previously pending claims satisfied the written description requirement. The Examiner rejected that argument on the ground that the claims and specification in that case differed from the claims and specification in this. Of course, no two claims sets or specifications are ever exactly the same. Applicant therefore offers the following close analysis.

The claim at issue in *Invitrogen* read:

1. An isolated polypeptide having DNA polymerase activity and substantially reduced RNAse H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the groups consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents.

The claim therefore included *no* structural limitations at all. The specification supporting the claim had only *a single example* of a polymerase having the recited activity. The court, however, found that the claim met the written description requirement because:

(1) at the time of the invention, the sequences of RT genes were known;

(2) members of the RT gene family shared significant homologies from one species to another

(3) the written description teaches that the invention can be applied to RT genes of other retroviruses including HTLV-1, BLV, RSV, and HIV;

(4) the specification cites references providing the known nucleotide sequences of these RT genes.

A comparison between the *Invitrogen* claims/support and the present application claims/support clearly reveals that, under the standard set forth in *Invitrogen* (which of course is binding on the Patent and Trademark Office), the present claims clearly satisfy the written description requirement.

As an initial matter, Applicant notes that the pending claims include *explicit* recitation of structural features (overall homology plus presence of a particular motif linked to the relevant activity). Furthermore, the present specification includes not one (as was the case in *Invitrogen*) but *six* examples of different DNA polymerases that fall within the scope of the claims used in the methods of the claims. Applicant also points out that:

(1) at the time of the invention, the sequences of many DNA polymerase genes were known, just like in *Invitrogen*;

(2) members of the DNA polymerase gene family share significant homologies from one species to another. This feature is well set out in the present specification (not just in the literature, as was the case in *Invitrogen*; see, for example, page 3, lines 8-21; see also page 10, line 12 – page 15, line 34). Furthermore, the present claim is limited to those DNA polymerases that in fact show both a recited degree of overall homology and a recited degree of identity with regard to a particular 15 amino acid motif. It is worth noting that the "family" of reverse transcriptase enzymes embraced by the *Invitrogen* is not nearly as structurally conserved as the set of DNA polymerases encompassed by the present claims

(3) the written description in the present case teaches that the invention can be applied to DNA polymerases other than the ones specifically exemplified, just as was the case with *Invitrogen* (see, for example, page 19, line 15, which reads "The similarity of incorporation patterns with these selected enzymes suggests that not only these archaeon DNA polymerases, but a larger family of DNA polymerases could share the ability to incorporate acyclo to a greater extent than dideoxy terminators"); and

(4) the specification cites references providing the known sequences of such other DNA polymerases (see, for example, page 10, line 22; page 14, line 18; page 14, line 19; page 15, lines 19-24).

Thus, with regard to every relevant fact relied upon by the court, the present case has at least as much, and in many cases *more* description than was present in *Invitrogen*. This description supports a claim that itself includes *more precision* than was present in *Invitrogen*. There can be no conclusion except that the present case meets the written description requirement. Should the Examiner disagree, Applicant respectfully requests that he specifically point out what further description would be required in order to support the present claims.

Invitrogen is not the only relevant legal standard. The Examiner has encouraged Applicant to consider the Written Description guidelines when crafting claims. Applicant has done so and submits that the presently presented claims clearly meet the requirements of those guidelines.

The most relevant Example in the written description guidelines is Example 14. The claim at issue in Example 14 is:

A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B.

Relevant features of the specification are:

(1) specification contemplates but does not exemplify variants of the protein (substitutions, deletions, insertions, additions);

(2) specification indicated that procedures for making variants are routine and provides an assay for detecting the catalytic activity.

It is also relevant to note that "having" language is "open" language so that, as confirmed in the Guidelines, the claim encompasses any protein that includes a sequence 95% identical to SEQ ID NO:3.

The present claim recites use of a protein that shows 30% *overall* identity with SEQ ID NO:4 *plus* at least 80% identity with a key motif involved in the relevant activity. Thus, the *motif* in the present claims is analogous to the SEQ ID NO:3 in the example claim from the Guidelines. The present claims require a lower percentage, but of a stricter comparator (identity vs homology). Moreover, the present claims have a further requirement of 30% overall identity with a larger sequence. Applicant therefore submits that, if the claim presented in example 14 of the Written Description Guidelines is supported, then the present claims must be.

In prior Office Actions, the Examiner has states that "Applicants recited structure and more so, the structure to function correlation, is insufficient to adequately describe the claimed genus of methods". Applicant respectfully challenges this assertion. *Every* DNA polymerase tested that has the recited structural characteristics has the recited activity. Applicant has therefore shown 100%. The Examiner has not provided any reason to doubt that other DNA polymerases with the recited characteristics would not also have this activity.

For all of these reasons, it is clear that the present claims meet the Written Description requirement. Furthermore, Applicant points out that the present claims are directed to a *method of use* of a known set of DNA polymerases. By contrast with both *Invitrogen* and the Written Description guidelines, the invention being claimed here is not the DNA polymerases themselves, but rather a new use for those polymerases based on a newly discovered *activity*.

Enablement

As with the written description rejection, the rejection for lack of enablement that was levied against the prior claims is mooted by the cancellation of those claims. However, the Examiner has indicated that it would be helpful if Applicant set out a "full Wands analysis" with regard to the new claims. Applicant therefore addresses each of

the Wands factors below, according to the groupings assigned to them by the Examiner in the Office Action of June 1, 2007:

Factors (4) Nature of the Invention and (8) Breadth of the Claims: Applicant has previously argued that DNA extension reactions are well within the skill of those of ordinary skill, and the Examiner has argued that incorporation of acyclonucleotides may not be. Applicant respectfully submits that the *invention* is not the extension reaction. The *invention* is the discovery that archeaon DNA B polymerases can incorporate acyclonucleotides, and indeed can incorporate them preferentially. Having established that they can, and further having shown that *six different such DNA polymerases* all can, Applicants have taught those skilled in the art that other polymerases of the class are likely also to have that activity.

Factors (5) State of the Prior Art and (7) Predictability of the Art: Applicant and Examiner are in agreement that the prior art with regard to DNA polymerases and their classifications is extensive. The Examiner questions "predictability of the art . . . as to the basis of those claimed archaeon DNA polymerases that are able to incorporate acyclonucleotides". Applicant agrees that the prior art itself does not contain such predictions. However, given that the prior art establishes the family of DNA polymerases and the present invention establishes that *all members tested* have the activity, Applicant respectfully submits that the claims are enabled.

Factors (1) Quantity of Experimentation Necessary; (2) Amount of Direction or Guidance; and (3) Presence or Absence of Working Examples: The Examiner does not challenge that one of ordinary skill could make and test all polypeptides within the scope of the claim to determine their ability to extend a DNA primer or incorporate acyclonucleotides (including to determine their ability to preferentially select acyclonucleotides as compared with alternatives). However, the Examiner maintained with regard to the previously pending claims that "it remains that [Applicants] have not enabled one of ordinary skill in the art to make and use those [DNA polymerases] having the necessary acyclonucleotide incorporation properties". Unfortunately, it is difficult for Applicant to respond to this accusation, as it is merely a statement of a conclusion (i.e., a conclusion of no enablement). The Examiner has not articulated why the existing description and evidence provided might be insufficient; nor has the Examiner identified

any particular information or evidence that Applicant would need to provide in order to satisfy the enablement requirement in the Examiner's view. This notwithstanding, Applicant respectfully submits that the present claims, which explicitly recite a key sequence motif as well as an overall degree of identity (thereby setting a boundary defining how closely related relevant polymerases must be to those whose activity Applicant has *expressly exemplified*.

Factor (6) Relative Skill of those in the Art: Applicant and Examiner agree that the relative skill of those in the art is very high. Indeed, the Examiner offers that it may be as high as PhD level.

For all of these reasons, Applicant respectfully submits that the present claims meet the enablement requirement.

In light of these Remarks and Amendments, Applicant submits that the present application is in condition for allowance. A notice to that effect is respectfully requested. If the Examiner believes a telephone call would be useful in expediting prosecution of this application, the undersigned invites the Examiner to call him at the number below.

Please charge any fees associated with this response, or apply any credits, to our Deposit Account Number 03-1721.

Respectfully submitted,

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